DN

ANDA 74-940

Lipha Pharmaceuticals, Inc.
U.S. Agent for: Alphapharm Pty. Ltd.
Attention: Bruce Goddard
9 West 57th Street, Suite 3825
New York, NY 10019-2701

Dear Sir:

This is in reference to your abbreviated new drug application dated July 25, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clonazepam Tablets USP, 0.5 mg, 1 mg and 2 mg.

Reference is also made to your amendments dated September 27, 1996; and March 7, June 12, June 13, September 30, and October 28, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Clonazepam Tablets 0.5 mg, 1 mg, and 2 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Klonopin Tablets 0.5 mg, 1 mg and 2 mg, respectively, of Hoffmann La Roche Inc). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW No 2

2. ANDA 74-940

3. NAME AND ADDRESS OF APPLICANT

Lipha Pharmaceuticals Inc.
Agent for: Alphapharm Pty. Ltd
9 West 57th Street, Suite 3825
New York, NY 10019-2701

4. LEGAL BASIS FOR SUBMISSION

The reference drug product is Klonopin Tablets 0.5, 1, and 2 mg marketed by Roche Laboratories.

The firm includes the patent certification as per Section 505 (j) (2) (A) (vii) (III) of the FDC act (p.10) and the exclusivity statement (p. 12).

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clonazapan Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Date of Application;	July 25, 1996
Amendment (N.C.):	September 23, 1996
Amendment:	September 27, 1996
FDA, acknowledgement:	October 8, 1996
FDA deficiency facsimile:	February 14, 1997
Amendment (response):	March 7, 1997
Amendment:	June 13, 1997

10. PHARMACOLOGICAL CATEGORY

Treatment of the Lennox-Gastaut syndrome (petit mal variant)

11. Rx or OTC

Rx.

12. RELATED IND/NDA/DMF(s)

NDA 17-533 Klonofin (Clonazepan) 0.5, 1 mg and 2 mg, Roche

13. DOSAGE FORM

Tablets

14. POTENCY

0.5 mg, 1 mg and 2 mg.

15. CHEMICAL NAME AND STRUCTURE

Clonazepam, $C_{15}H_{10}ClN_3O_3$

16. RECORDS AND REPORTS

The firm includes the certification against the use of debarred person(s) (p. 3641), and certifies that no persons with "relevant convictions or not debarred have not been associated in any way with this ANDA" (p. 3642).

17. COMMENTS

In response to the Agency's request the firm explains that the expiration date for the bulk is 6 months from the date of manufacture, and the expiration date for the marketed packaged product is 24 months from the date of manufacture. Additionally the firm commits to conduct stability testing on the bulk product stored in containers, at 3 and 6 months on the first three commercial batches and one batch each year thereafter.

The data will be provided to the Agency in the annual report.

18. CONCLUSIONS AND RECOMMENDATIONS

Issue an approval letter.

19. REVIEWER: DATE COMPLETED:

A. Croitoru June 17, 1997

UNIT DOSE 100 tablets NDC 57315-017-04

CLONAZEPAM TABLETS USP 0.5 mg

IV

CHILD RESISTANT PACKAGE

USUAL DOSAGE: For dosage recommendations and other important prescribing information read accompanying insert.

STORE AT 15° TO 30°C (59° TO 86°F)

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia

Call 1-800-661 3429 1739

UNIT DOSE 100 tablets NDC 57315-017-04

CLONAZEPAM TABLETS USP 0.5 mg

IV

Lot No.:
Exp.

0.5 mg

CLONAZEPAM TABLETS USP IV

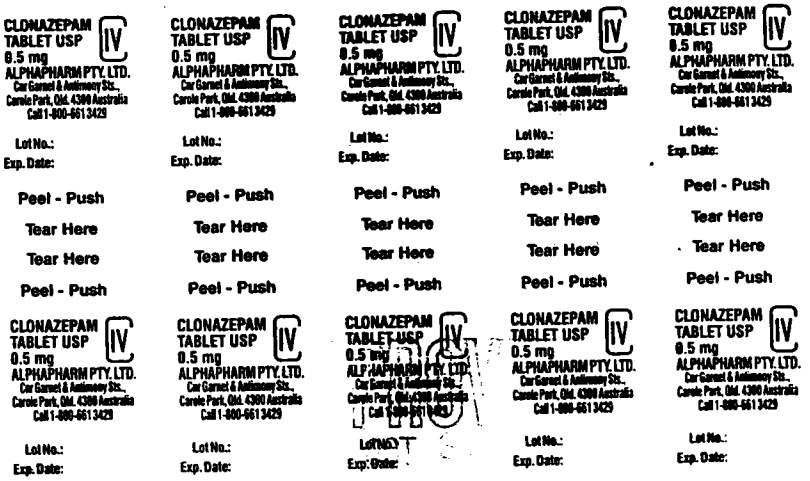
UNIT DOSE 100 tablets NDC 57315-017-04

UNIT DOSE 100 tablets NDC 57315-017-04

CLONAZEPAM TABLETS USP IV 0.5 mg

ALPHAPHARM

CAUTION: Federal Law Prohibits Dispensing Without Prescription


CLONAZEPAM
TABLET USP
0.5 mg
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300 Australia
Call 1-800-661 3429
Lot No.:
Exp. Date:
Peel - Push
Tear Here
Tear Here
Peel - Push

Each tablet contains
Clonazepam, USP 1 mg

USUAL DOSAGE:
For dosage recommendations and other important prescribing information, read accompanying insert.

1746
Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia
Call 1-800-661 3429

NDC 57315-018-01

ALPHAPHARM

CLONAZEPAM TABLETS USP

IV

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Lot No.:

Exp. Date:

STORE AT 15° TO 30°C (59° TO 86°F).

Dispense in tight, light-resistant containers as defined in USP/NF.

Bulk package - Not intended for Dispensing.

Each tablet contains
Clonazepam, USP 2 mg

USUAL DOSAGE:
For dosage recommendations and other important prescribing information, read accompanying insert.

1748
Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia
Call 1-800-661 3429

NDC 57315-019-01

ALPHAPHARM

CLONAZEPAM TABLETS USP

IV

2 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Lot No.:

Exp. Date:

STORE AT 15° TO 30°C (59° TO 86°F).

Dispense in tight, light-resistant containers as defined in USP/NF.

Bulk package - Not intended for Dispensing.

Each tablet contains
Clonazepam, USP 2 mg

USUAL DOSAGE:
For dosage recommendations and other important prescribing information, read accompanying insert.

1749

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia

Call 1-800-661 3429

NDC 57315-019-02

ALPHAPHARM

CLONAZEPAM TABLETS USP

IV

2 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Lot No.:

Exp. Date:

STORE AT 15° TO 30°C (59° TO 86°F).

Dispense in tight, light-resistant containers as defined in USP/NF.

Bulk package - Not intended for Dispensing.

UNIT DOSE 100 tablets NDC 57315-019-04

CLONAZEPAM TABLETS USP 2 mg

IV

CHILD RESISTANT PACKAGE

USUAL DOSAGE: For dosage recommendations and other important prescribing information read accompanying insert.

STORE AT 15° TO 30°C (59° TO 86°F)

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia

Call 1-800-661 3429 1741

UNIT DOSE 100 tablets NDC 57315-019-04

CLONAZEPAM TABLETS USP 2 mg

IV

Lot No.:
Exp.

2 mg

CLONAZEPAM TABLETS USP IV

UNIT DOSE 100 tablets NDC 57315-019-04

UNIT DOSE 100 tablets NDC 57315-019-04

CLONAZEPAM TABLETS USP IV

2 mg

ALPHAPHARM

CAUTION: Federal Law Prohibits Dispensing Without Prescription

Each tablet contains
Clonazepam, USP 0.5 mg

USUAL DOSAGE:
For dosage recommendations and other important prescribing information, read accompanying insert.

1743

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia

Call 1-800-661 3429

NDC 57315-017-02

ALPHAPHARM

CLONAZEPAM TABLETS USP

C IV

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Lot No.:

Exp. Date:

STORE AT 15° TO 30°C (59° TO 86°F).

Dispense in tight, light-resistant containers as defined in USP/NF.

Bulk package - Not Intended for Dispensing.

Each tablet contains
Clonazepam, USP 1 mg

USUAL DOSAGE:
For dosage recommendations and other important prescribing information, read accompanying insert.

1747

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia

Call 1-800-661 3429

NDC 57315-018-02

ALPHAPHARM

CLONAZEPAM TABLETS USP

C IV

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Lot No.:

Exp. Date:

STORE AT 15° TO 30°C (59° TO 86°F).

Dispense in tight, light-resistant containers as defined in USP/NF.

Bulk package - Not Intended for Dispensing.

Each tablet contains
Clonazepam, USP 2 mg

USUAL DOSAGE:
For dosage recommendations and other important prescribing information, read accompanying insert.

1748

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia
Call 1-800-661 3429

NDC 57315-019-01

ALPHAPHARM

CLONAZEPAM TABLETS USP

C IV

2 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

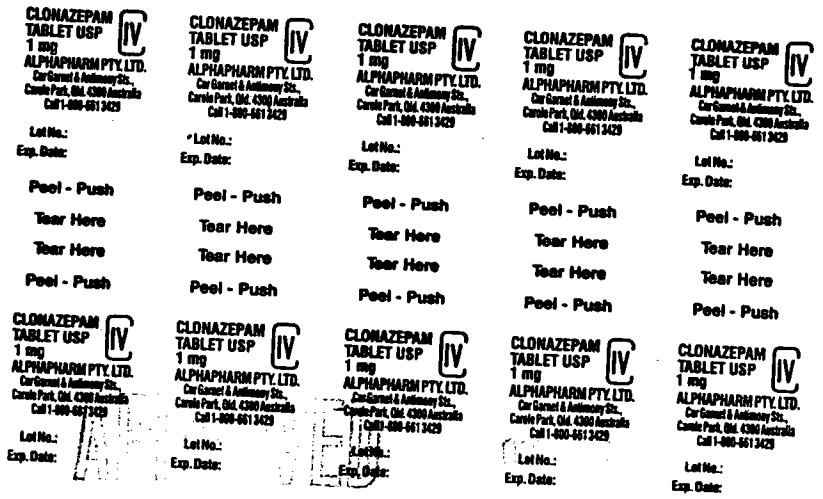
Lot No.:

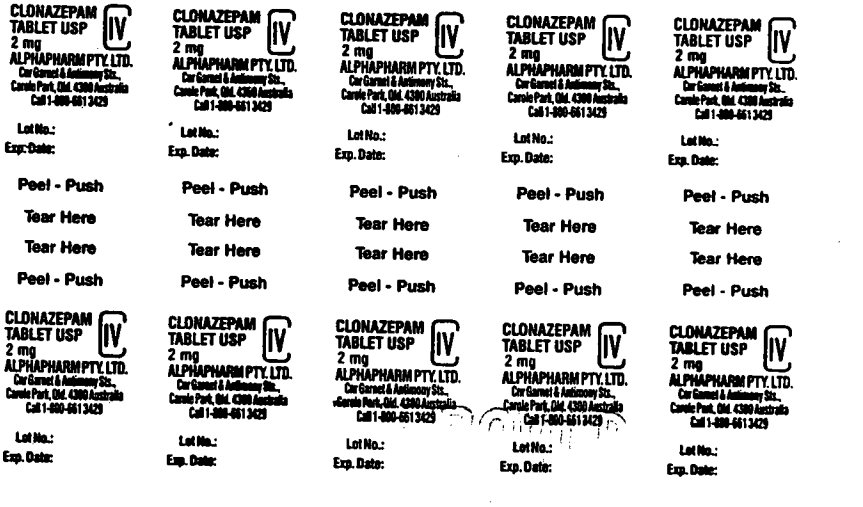
Exp. Date:

STORE AT 15° TO 30°C (59° TO 86°F).

Dispense in tight, light-resistant containers as defined in USP/NF.

Bulk package - Not Intended for Dispensing.


CLONAZEPAM
TABLET USP
1 mg
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300 Australia
Call 1-800-661 3429
Lot No.:
Exp. Date:
Peel - Push
Tear Here
Tear Here
Peel - Push


CLONAZEPAM
TABLET USP
2 mg
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300 Australia
Call 1-800-661 3429
Lot No.:
Exp. Date:
Peel - Push
Tear Here
Tear Here
Peel - Push

UNIT DOSE 100 tablets NDC 57315-018-04

CLONAZEPAM TABLETS USP 1 mg

IV

CHILD RESISTANT PACKAGE

USUAL DOSAGE: For dosage recommendations and other important prescribing information read accompanying insert.

STORE AT 15° TO 30°C (59° TO 86°F)

Manufactured by:
ALPHAPHARM PTY. LTD.
Cnr Garnet & Antimony Sts.,
Carole Park, Qld. 4300
Australia

Call 1-800-661 3429 1740

UNIT DOSE 100 tablets NDC 57315-018-04

CLONAZEPAM TABLETS USP 1 mg

IV

Lot No.:
Exp.

1 mg

CLONAZEPAM TABLETS USP IV

UNIT DOSE 100 tablets NDC 57315-018-04

UNIT DOSE 100 tablets NDC 57315-018-04

CLONAZEPAM TABLETS USP 1 mg

IV

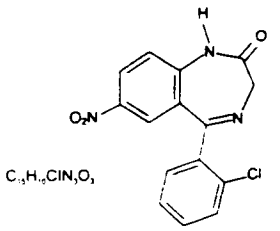
ALPHAPHARM

CAUTION: Federal Law Prohibits Dispensing Without Prescription

CLONAZEPAM TABLETS USP

DESCRIPTION: Each tablet, for oral administration contains 0.5 mg, 1 mg or 2 mg clonazepam. Each tablet also contains lactose monohydrate, microcrystalline cellulose, corn starch, pregelatinised corn starch and magnesium stearate with the following dye systems: 0.5 mg - D&C Yellow No. 10; 1 mg - D&C Yellow No. 10 and FD&C Yellow No. 6.

Chemically, clonazepam is 5-(*0*-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one. It is a light yellow crystalline powder. It has a molecular weight of 315.72 and the following structural formula:



$C_{15}H_{10}ClN_3O_3$

CLINICAL PHARMACOLOGY: In laboratory animals, Clonazepam exhibits several pharmacologic properties which are characteristic of the benzodiazepine class of drugs. Convulsions produced in rodents by pentylenetetrazol or electrical stimulation are antagonized, as are convulsions produced by photic stimulation in susceptible baboons. A taming effect in aggressive primates, muscle weakness and hypnosis are likewise produced by Clonazepam. In humans it is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

Single oral dose administration of Clonazepam to humans gave maximum blood levels of drug, in most cases, within one to two hours. The half-life of the parent compound varied from approximately 18 to 50 hours, and the major route of excretion was in the urine. In humans, five metabolites have been identified. In general, the biotransformation of clonazepam followed two pathways: oxidative hydroxylation at the C-3 position and reduction of the 7-nitro function to form 7-amino and/or 7-acetyl-amino derivatives.

INDICATIONS AND USAGE: Clonazepam tablets are useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. In patients with absence seizures (petit mal) who have failed to respond to succinimides, Clonazepam may be useful.

In some studies, up to 30% of patients have shown a loss of anticonvulsant activity, often within three months of administration. In some cases, dosage adjustment may reestablish efficacy.

CONTRAINDICATIONS: Clonazepam should not be used in patients with a history of sensitivity to benzodiazepines, nor in patients with clinical or biochemical evidence of significant liver disease. It may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow angle glaucoma.

WARNINGS: Since Clonazepam produces CNS depression, patients receiving this drug should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle. They should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during Clonazepam therapy (see Drug Interactions).

Usage in Pregnancy: The effects of Clonazepam in human pregnancy and nursing infants are unknown.

Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans: the possibility also exists that other factors, e.g., genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

These considerations should be weighed in treating or counseling epileptic women of childbearing potential.

Use of Clonazepam in women of childbearing potential should be considered only when the clinical situation warrants the risk. Mothers receiving Clonazepam should not breast feed their infants.

In a two-generation reproduction study with Clonazepam given orally to rats at 10 or 100 mg/kg/day, there was a decrease in the number of pregnancies and a decrease in the number of offspring surviving until weaning. When Clonazepam was administered orally to pregnant rabbits at 0.2, 1, 5 or 10 mg/kg/day, a nondose-related incidence of cleft palates, open eyelids, fused sternebrae and limb defects was observed at the 0.2 and 5 mg/kg/day levels. Nearly all of the malformations were seen from one dam in each of the affected dosages.

Usage in Children: Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of Clonazepam is important in pediatric patients.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines. (See DRUG ABUSE AND DEPENDENCE section.)

PRECAUTIONS: When used in patients in whom several different types of seizure disorders coexist, Clonazepam may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and clonazepam may produce absence status.

Periodic blood counts and liver function tests are advisable during long term therapy with Clonazepam.

The abrupt withdrawal of Clonazepam, particularly in those patients on long-term, high-dose therapy, may precipitate

status epilepticus. Therefore, when discontinuing Clonazepam, gradual withdrawal is essential. While Clonazepam is being gradually withdrawn, the simultaneous substitution of another anticonvulsant may be indicated. Metabolites of Clonazepam are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

Clonazepam may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, Clonazepam should be used with caution in patients with chronic respiratory diseases.

Information for Patients: To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

ADVERSE REACTIONS: The most frequently occurring side effects of Clonazepam are referable to CNS depression. Experience to date has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients. Others, listed by system, are:

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, "glassy-eyed" appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo.

Psychiatric: Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis, suicidal attempt (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances).

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages.

Cardiovascular: Palpitations.

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema.

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, hepatomegaly, increased appetite, nausea, sore gums.

Genitourinary: Dysuria, enuresis, nocturia, urinary retention.

Musculoskeletal: Muscle weakness, pains.

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain.

Hemaopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia.

Hepatic: Transient elevations of serum transaminases and alkaline phosphatase.

DRUG ABUSE AND DEPENDENCE: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving clonazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

DRUG INTERACTIONS: The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

OVERDOSAGE: Symptoms of Clonazepam overdosage, like those produced by other CNS depressants, include somnolence, confusion, coma and diminished reflexes. Treatment includes monitoring of respiration, pulse and blood pressure, general supportive measures and immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Methylphenidate or caffeine and sodium benzoate may be given to combat CNS depression. Dialysis is of no known value.

DOSAGE AND ADMINISTRATION: *Infants and Children:* Clonazepam is administered orally. In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses. Dosage should be increased by no more than 0.25 to 0.5 mg every third day until a daily maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into three equal doses. If doses are not equally divided, the largest dose should be given before retiring.

Adults: The initial dose for adults should not exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of 0.5 to 1 mg every three days until seizures are adequately controlled or until side effects preclude any further increase. Maintenance dosage must be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg.

The use of multiple anticonvulsants may result in an increase of depressant adverse effects. This should be considered before adding Clonazepam to an existing anticonvulsant regimen.

HOW SUPPLIED: Clonazepam Tablets are available as follows:

0.5 mg (Light yellow, round, scored $\frac{CN}{0.5}$ one side; G on reverse)	
Bottles of 100	NDC 57315-017-01
Bottles of 500	NDC 57315-017-02
Unit Dose of 100	NDC 57315-017-04
1 mg (Dark Yellow, round, scored $\frac{CN}{1}$ one side; G on reverse)	
Bottles of 100	NDC 57315-018-01
Bottles of 500	NDC 57315-018-02
Unit Dose of 100	NDC 57315-018-04
2 mg (White, round, scored $\frac{CN}{2}$ one side; G on reverse)	
Bottles of 100	NDC 57315-019-01
Bottles of 500	NDC 57315-019-02
Unit Dose of 100	NDC 57315-019-04

MANUFACTURED BY:

Alphapharm Pty Ltd
Cnr Garnet & Antimony Sts.,
Carole Park. Qld. 4300
Australia

1814
Revised March 1996

Call 1-800-661 3429

ANDA 74-940

Lipha Pharmaceuticals, Inc.
U.S. Agent for: Alphapharm Pty. Ltd.
Attention: Anita M. Goodman, M.D.
9 West 57th St., Suite 3825
New York NY 10019-2701

JAN 15 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Clonazepam Tablets USP, 0.5 mg, 1 mg and 2 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT - 3 1997

Clonazepam Tablets
1 mg
ANDA # 74-940
Reviewer: Man M. Kochhar

Alphapharm Pty. Ltd.
New York, NY
Submission Date:
September 30, 1997

Response to the Fax

Background:

The Division of Bioequivalence requested the sponsor to show the reasons for for subject # 5. They have responded to our request and provided the reasons for not including subject # 5 data.

Comment:

The data for subject # 5 was not reported due to poor in Phase II. For subject # 5, the was approximately These findings were confirmed with and without Therefore, Phase II data were not reportable.

The reviewer agrees with the conclusion drawn by the firm and therefore, the results in the submission are acceptable. The recommendation in the original submission will not change. The study is acceptable.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence.

RD INITIALLED RMHETRE
FT INITIALLED RMHATRE

Ramakant M. Mhatre, Ph.D. 10/3/97
Chief, Review Branch III

Concur: Date: 10/3/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

TELEPHONE MEMO

To: Bruce Guddard, Alpharm PTY 212-223-1399

REF # 74-940 Clonazepam

From: Nancy Chamberlin NC

Date: 9-29-97

Subject: **Chromatograms**

Requested by: Rabi Patnaik

I called him to check on the information we requested in August on
He was out of the office, but agreed to call me the next day.

9/30- He said they had faxed it on 8-21-97, but never submitted it to the ANDA jacket. He agreed to re-fax it and to submit it to the ANDA.

JAN - 8 1997

JAN - 8 1997

Clonazepam Tablets, 0.5 mg, 1 mg and 2 mg
ANDA # 74-940
Reviewer: Man M. Kochhar
74940SWD.796

Alphapharm Pty Ltd.
New York, NY
Submission Date:
July 25, 1996

Review of a Bioequivalence Study, a Waiver Request and Dissolution

I. BACKGROUND

Clonazepam is a benzodiazepine with a pharmacological profile similar to other anxiolytic/sedative benzodiazepines. It is indicated for the management of myoclonic or akinetic seizures and Lannox-Gastaut syndrome.

Clonazepam is 98% absorbed and extensively metabolized with a half-life of about 18-50 hours. Less than 1% of an oral dose is excreted in the urine. The drug is 86% plasma protein bound.

The innovator product [Klonopin Tablets (Roche)] is available in 3 strengths 0.5, 1 and 2 mg. Due to side effects (drowsiness, ataxia, personality changes, etc.), the recommended adult dose is 1.5 mg daily in 3 divided doses. Doses may be increased by 0.5 - 1 mg every 3 days until seizures are controlled.

II. OBJECTIVE

The objective of this study is to determine whether Alphapharm's 2.0 mg clonazepam tablets are bioequivalent to Roche (Klonopin) clonazepam tablets 2.0 mg under single dose fasting conditions. The firm is requesting a waiver for 0.5 mg and 1.0 mg tablet based on an acceptable 2 mg bioequivalence study under fasting conditions.

III. IN-VIVO STUDY

The Purpose of this study is to assess the bioequivalence of two formulations of clonazepam 2 mg tablet by Alphapharm, compared with Klonopin 2 mg tablet by Roche when given under fasting conditions.

The bioequivalence study was conducted at
under the supervision of

IV. STUDY DESIGN

The study was designed as a randomized, single dose, two-way crossover bioequivalence study in 28 healthy volunteers under

fasting conditions.

Number of Subjects: 28 healthy male volunteers were enrolled in the study. 25 subjects completed the study. Subject #7 and 8 did not show up for phase 2 for personal reason and data for subject # 5 was not included because of

Treatments: A. Test: 1 x 2 mg tablet (Alphapharm clonazepam lot # NE071) with 240 mL of water.

Batch Size: Expiration Date: 5/97
Potency:101.7 %; Content Uniformity:99.3 %

B. Reference: 1 x2 mg tablet Klonopin,(Roche lot # 3045) with 240 mL of water.

Expiry: 8/97; Potency:97.5%
Content Uniformity: 101.1%

Blood Samples: Samples were collected in Vacutainers containing heparin before dosing (10 mL) and at 0.33, 0.67, 1,1.33, 1.67, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36,48, 72, 96, 120, and 144 hours after dosing.

Fasting/Meals: Fast for 10 hours before dosing and 4 hours after dosing. Meals or snacks were served at 4 hours after dosing, and at appropriate times thereafter; meal plans identical for both periods. Water was permitted ad lib. until 1 hour before dosing and one hour after dosing.

Housing: From 10 hours before dosing until after the collection of 48 hours blood sample. Subjects returned to the facility for the subsequent 4 blood drawings.

Washout Period: 14 days between doses.

Analytical Method:

Subject Screening:

The study involved volunteers between the ages of 18-50, and within ±10% of their frame and size according to Metropolitan Life Insurance Company Bulletin,1983. The subjects were selected for this study after i) physical examination, ii) medical and complete laboratory tests (blood chemistry, hematology, urinalysis, etc.). The volunteers were instructed not to take any prescription medications and/or OTC preparations for at least one

week prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 48 hours prior to dosing and during the periods when blood samples being collected. Each subject signed a written informed consent form.

Pharmacokinetic and Statistical Analysis:

Plasma concentration-time profiles of clonazepam were analyzed pharmacokinetically and statistically to evaluate relative bioavailability of test product to reference product. Significance of differences due to treatments, phase, dosing and sequence were evaluated for plasma clonazepam concentrations at each sampling time and Cmax, Tmax, Kel, t1/2 and AUC by ANOVA using SAS (GLM procedure).The power to detect 20% differences between formulations (t-test method), and 90% confidence intervals (two,one-sided t-test method) were calculated for each major pharmacokinetic parameters.

ASSAY VALIDATION

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, sequence and subjects within sequence) were carried out to compare formulations at each sampling time, AUC (0-t), AUC (inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test method) were calculated for clonazepam pharmacokinetic parameters. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Of the 28 subjects enrolled in the study, 25 completed the crossover. Subject # 7 and 8 did not show up for Phase 2 and subject # 5 was dropped due to The plasma samples from 25 subjects were assayed for clonazepam as per the protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of clonazepam are given in Table 1 and 2. The mean plasma clonazepam concentrations are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Clonazepam (N=25)

Time (hours)	Alphapharm's Clonazepam Lot # NE071 ng/mL (CV%)	Roche's Klonopin Lot # 3045 ng/mL (CV%)	T/R
0	0 (-)	0 (-)	0.0
0.33	0.20 (80)	0.15 (72)	1.33
0.67	2.79 (46)	3.43 (49)	0.81
1	4.71 (34)	6.53 (39)	0.72
1.33	6.81 (26)	7.55 (32)	0.91
1.67	7.04	7.90	0.89
2	7.74 (22)	8.02 (25)	0.96
2.5	8.09 (19)	8.53 (22)	0.95
3	8.37 (18)	8.67 (19)	0.96
3.5	8.53 (17)	8.58 (17)	0.99
4	8.59 (16)	8.78 (17)	0.98
6	7.37 (17)	7.32 (16)	1.01
8	6.92 (18)	6.94 (15)	0.99
12	6.10 (18)	6.04 (16)	1.01
24	4.93 (17)	4.79 (17)	1.03
36	4.26 (17)	4.15 (17)	1.03
48	3.20 (18)	3.31 (17)	0.97
72	2.13 (18)	2.04 (16)	1.04
96	1.41 (22)	1.34 (20)	1.05
120	0.91 (28)	0.85 (30)	1.07
144	0.59 (59)	0.60 (59)	0.98

Table 2

A Summary of Clonazepam Pharmacokinetic Parameters for 25 subjects

Parameters	Alphapharm's Clonazepam (CV%)	Roche's Klonopin (CV%)	T/R
AUC_{0-144} ng.hr/mL	399.76 (15)	395.55 (14)	1.01
AUC_{0-inf} ng.hr/mL	434.45 (17)	431.63 (15)	1.01
C_{max} ng/mL	9.31 (18)	9.87 (17)	0.94
T_{max} (hours)	2.99 (42)	2.51 (50)	1.19

$t_{1/2}$ (hours)	38.16 (20)	39.69 (22)	0.96	
K_{el} (1/hour)	0.019 (19)	0.018 (21)	1.05	
Ln AUC_{0-144} ng.hr/mL	5.98 (2)	5.97 (2)	1.01	**CI Intervals** 97; 105
Ln AUC_{inf} ng.hr/mL	6.06 (3)	6.06 (3)	1.00	97; 104
Ln C_{max} ng/mL	2.22 (8)	2.27 (8)	0.97	89; 99

The clonazepam AUC_{0-t} and AUC_{0-inf} produced by Alphapharm's formulation were 1.06% higher and 0.65% higher respectively than the values for the reference drug. The C_{max} was 5.6% lower than the reference. T_{max} was 19.1% higher for the test drug. $t_{1/2}$ and K_{el} values differ only by less than 5%. ANOVA performed on the plasma clonazepam concentration data at each of the twenty one sampling times detected statistically significant differences at 0.33 hour between the two formulations. The firm did calculate Ln AUC and Ln Cmax for clonazepam and the 90% confidence intervals for log-transformed parameters were 97 to 105 for Ln AUC0-t, 97 to 104 for Ln AUCinf, and 89 to 99 for Ln Cmax.

The ratios for clonazepam for AUC_{0-144} and AUC_{0-inf} and C_{max} were well within the limit of 0.8 to 1.2 for defining product bioequivalence, in a fasting study.

The central nervous system (CNS) depressant effect of clonazepam was observed in 25 subjects. There were no serious adverse effects which required dropping any subjects from the study or required therapeutic medical intervention.

On the basis of fasting <u>in vivo</u> bioavailability data it is determined that Alphapharm's clonazepam 2 mg tablets and Roche's Klonopin 2 mg tablets are bioequivalent under fasting conditions.

<u>DISSOLUTION TEST RESULTS:</u>

<u>In vitro</u> dissolution testing was conducted in 900 mL of water at 37°C using USP XXIII apparatus 2 (paddle) at 100 rpm. Results are presented in Table 3. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablets in 60 minutes. The batch size was tablets.

COMMENTS:

1. The study was conducted in 25 healthy volunteers comparing the plasma concentrations from Alphapharm's clonazepam 2 mg tablets to that of reference Klonopin 2 mg tablets manufactured by Roche. The clonazepam AUC_{0-144}, AUC_{0-inf}, C_{max} of the Alphapharm formulation were 1.06% higher, 0.65% higher, and 5.62% lower respectively than the corresponding Roche's reference values. ANOVA performed on the plasma clonazepam concentration data detected statistically significant differences at 0.33 hour between two formulations. These results indicate that the test drug is bioequivalent to the reference product under fasting conditions.

2. Analysis of variance indicated no statistical significant treatment differences or group-by-sequence effect for AUC and Cmax for clonazepam. The 90% confidence intervals were well within the limits of ±20%.

3. The validation studies conducted by the sponsor for clonazepam are acceptable to the Division of Bioequivalence.

4. The firm has not requested a waiver for 0.5 mg, and 1.0 mg clonazepam tablets.They have provided the dissolution and formula comparison for 0.5 mg, 1.0 mg and 2.0 mg tablets. I assumed that the reason for providing this information was to request a waiver for 0.5 mg and 1.0 mg tablets based on an acceptable fasting bioequivalence study on 2 mg tablet. Therefore, the waiver for 0.5 mg and 1 mg tablet is granted.

5 The in vitro dissolution testing conducted for 2 mg tablets of the test and reference products shows greater than of the labeled amount of the clonazepam dissolved in 60 minutes.

6. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

7. The in vivo fasting bioequivalence study is acceptable.

8. The firm has demonstrated that the formulations of its clonazepam tablets, 0.5 mg, 1.0 mg, and 2.0 mg are proportional with respect to active and inactive ingredients (Table 4).

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting bioequivalence study conducted by Alphapharm on its Clonazepam 2 mg tablets, lot # NE071, comparing it to Klonopin 2 mg tablets, lot # 3045 manufactured by Roche Inc. have been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Alphapharm's

Clonazepam-2 mg tablets are bioequivalent to the reference product, Klonopin 2 mg tablets manufactured by Roche.

2. The in vitro test results on the 0.5 mg, 1 mg and 2 mg strengths are acceptable. The formulations for 0.5 mg, and 1.0 mg Clonazepam tablets are proportionally similar to 2 mg Clonazepam tablet which underwent bioequivalent study. The waiver of in vivo bioequivalence study requirement for Alphapharms 0.5 mg and 1.0 mg tablets is granted. The 0.5 mg and 1.0 mg Clonazepam tablets from Alphapharm are therefore, deemed bioequivalent to 0.5 mg, and 1.0 mg Klonopin tablets manufactured by Roche based on 21 CFR 320.22 (d)(2).

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs.The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIII apparatus 2 (Paddle) at 100 rpm. The test should meet the following specifications:

> Not less thar of the labeled amount of the drug in the tablet is dissolved in 60 minutes.

4. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution test, and therefore, the application is acceptable.

The firm should be informed of the recommendations.

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MMKochhar/mmk/11-15-96; 12-24-96;74-940

cc: 74-940 original, HFD-600 (Hare), HFD-344 (CViswanathan), HFD-658 (Mhatre, Kochhar), Drug File, Division File

TABLE 3

DISSOLUTION

Drug: Clonazepam
ANDA # 74-940
Firm: Alphapharm
Submission Date: July 25, 1996

Conditions for Dissolution:

USP XXIII, Apparatus 2 (Paddle) at 100 rpm
No. of Units: 12
Medium: 900 mL of degassed water
Specifications: NLT n 60 minutes
Reference Drug: Klonopin by Roche

Results:

Sampling Times Minutes	**Clonazepam Lot # NF098 Strength 1 mg**			**Klonopin Lot # 2162 Strength 1 mg**		
	Mean%	**Range**	**RSD**	**Mean%**	**Range**	**RSD**
10	81		1.1%	70		4.1%
20	91		0.9%	90		2.3%
40	96		0.7%	98		2.1%
60	97		0.7%	102		1.1%
		Lot # NF095 Strength 0.5 mg			Lot # 1859 Strength 0.5 mg	
10	88		0.6%	52		2.2%
20	94		0.6%	86		2.4%
40	97		0.7%	97		2.5%
60	98		1.0%	99		4.2%
		Lot # NE071 Strength 2.0 mg			Lot # 3045 Strength 2.0 mg	
10	58		1.1%	59		3.0%
20	74		0.9%	83		1.0%
40	88		0.8%	96		1.1%
60	94		0.9%	99		0.9%

TABLE 4

Ingredients	**0,5 mg Tablet**	**1.0 mg Tablet**	**2.0 mg Tablet**
Clonazepam	0.5 mg	1.0 mg	2.0 mg
Microcrystalline Cellulose			
Lactose Monohydrate			
Maize Starch			
Magnesium Stearate			
Pregelatinised Starch			
D&C Yellow # 10			
FD&C Yellow # 6			
TOTAL TABLET WEIGHT	150.0 mg	150.0 mg	150.0 mg

MEAN PLASMA CLONAZEPAM CONCENTRATIONS

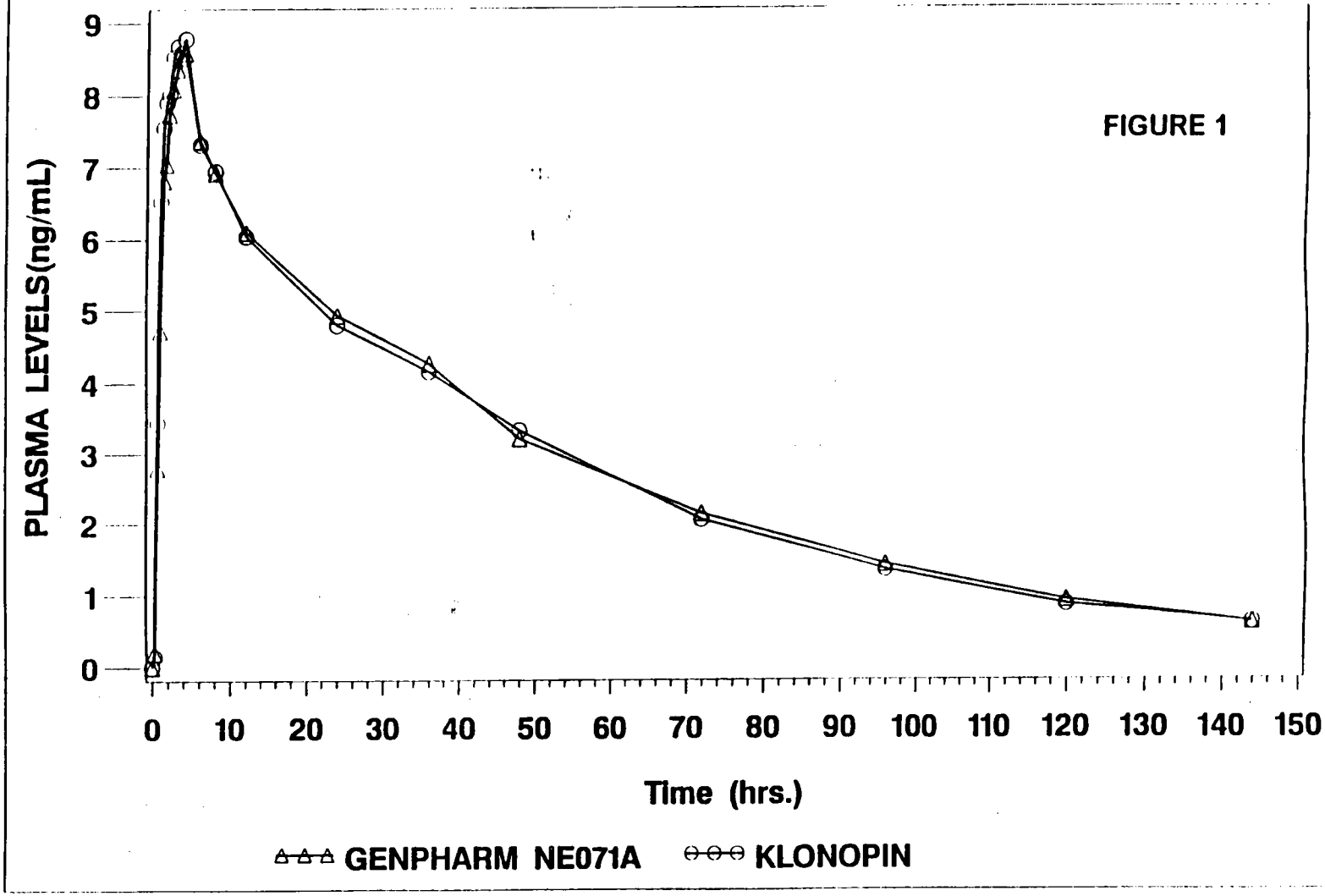

FIGURE 1